Intraoperative Methadone for the Prevention of Postoperative Pain

A Randomized, Double-blinded Clinical Trial in Cardiac Surgical Patients

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ABSTRACT

Background: The intensity of pain after cardiac surgery is often underestimated, and inadequate pain control may be associated with poorer quality of recovery. The aim of this investigation was to examine the effect of intraoperative methadone on postoperative analgesic requirements, pain scores, patient satisfaction, and clinical recovery.

Methods: Patients undergoing cardiac surgery with cardiopulmonary bypass (n = 156) were randomized to receive methadone (0.3 mg/kg) or fentanyl (12 μg/kg) intraoperatively. Postoperative analgesic requirements were recorded. Patients were assessed for pain at rest and with coughing 15 min and 2, 4, 8, 12, 24, 48, and 72 h after tracheal extubation. Patients were also evaluated for level of sedation, nausea, vomiting, itching, hypoventilation, and hypoxia at these times.

Results: Postoperative morphine requirements during the first 24 h were reduced from a median of 10 mg in the fentanyl group to 6 mg in the methadone group (median difference [99% CI], −4 [−8 to −2] mg; $P < 0.001$). Reductions in pain scores with coughing were observed during the first 24 h after extubation; the level of pain with coughing at 12 h was reduced from a median of 6 in the fentanyl group to 4 in the methadone group (−2 [−3 to −1]; $P < 0.001$). Improvements in patient-perceived quality of pain management were described in the methadone group. The incidence of opioid-related adverse events was not increased in patients administered methadone.

Conclusions: Intraoperative methadone administration resulted in reduced postoperative morphine requirements, improved pain scores, and enhanced patient-perceived quality of pain management. (ANESTHESIOLOGY 2015; 122:1112-22)

ACUTE postoperative pain is observed in a high percentage of cardiac surgical patients, particularly during the first 2 days after surgery.[1,2] Despite treatment with potent opioids, most patients have reported pain of a moderate to severe intensity during the intensive care unit (ICU) admission.[3–5] Multiple procedural factors contribute to pain after cardiac surgery, including surgical incisions, sternotomy, possible rib fractures, chest tube placement, and various intravascular cannulations. Inadequately treated pain may have adverse physiologic consequences that can impair clinical recovery in this patient population. An association between chest pain and pulmonary dysfunction has been observed, and sympathetic nervous system activation secondary to pain can induce myocardial ischemia and arrhythmias.[6,7] Therefore, appropriate pain management strategies can not only provide patient comfort but also attenuate adverse events after cardiopulmonary bypass (CPB).

During early recovery from cardiac surgery, intravenous opioids are typically administered to control pain, either by intermittent administration by nursing staff or by a patient-controlled analgesia device.[8–10] Repeated doses or boluses of analgesic medications can result in fluctuating blood opioid concentrations; clinical responses can vary from inadequate pain relief to serious side effects, such as respiratory arrest, with only relatively brief periods of high-quality pain relief. An alternative approach to intermittent administration of shorter-acting opioids, such as morphine or hydromorphone, is the use of a single dose of methadone. Methadone

What We Already Know about This Topic

- Pain experienced after cardiac surgery is often inadequately controlled, particularly during the early phases of recovery
- Methadone by virtue of its long half-life may provide superior control of pain after cardiac surgery

What This Article Tells Us That Is New

- Intraoperative methadone administration may be superior to intraoperative fentanyl for the control of pain during the 24-h period after cardiac surgery
- The superior pain control provided by methadone does not appear to involve a higher likelihood of opioid-related adverse events in this setting

This article is featured in "This Month in Anesthesiology," page 1A. Corresponding article on page 969.

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is a unique opioid with pharmacologic properties that may be advantageous in the setting of cardiac surgery. When administered at larger doses (20 to 30 mg), the duration of analgesia is ≈24 to 36 h.[11,12] Therefore, a single administration at induction of anesthesia may provide stable analgesia throughout the ICU admission (which corresponds to the time of highest reported pain scores). When used at doses of 0.2 to 0.3 mg/kg, methadone has not been associated with a higher incidence of opioid-related adverse events (compared with shorter-acting opioids).[11,13–16] In an animal model, methadone has potent cardioprotective properties, with a maximal opioid-induced myocardial salvage effect observed at a dose of 0.3 mg/kg.[17] Finally, chronic postoperative pain has been reported in 30 to 40% of patients in the first year after cardiac surgery.[5,18] Methadone may reduce the development of chronic pain by more effectively controlling acute pain after surgery, as well as by acting as an antagonist at the N-methyl-D-aspartate (NMDA) receptor.[19] The primary aim of this randomized, double-blind clinical trial was to determine the effects of methadone on analgesic requirements and pain scores after cardiac surgery with CPB, compared with patients administered standard doses of fentanyl. In addition, the effects of methadone on patient satisfaction scores, markers of myocardial injury, hemodynamic parameters, postoperative intubation times, and other measures of clinical recovery were determined. Our joint primary hypothesis was that patients administered intraoperative methadone would have both decreased morphine requirements in the first 24 h after cardiac surgery and improved pain scores at 12 h after extubation when compared with patients administered standard intraoperative doses of fentanyl. Our secondary hypothesis was that patients administered methadone would be more satisfied with their pain management in the first 24 h after surgery than those administered fentanyl.

Materials and Methods

Study Population and Perioperative Management

This clinical trial was approved by the NorthShore University HealthSystem Institutional Review Board (USA), and written informed consent was obtained from all patients. The study was conducted at a single tertiary medical center (NorthShore University HealthSystem) affiliated with the University of Chicago Pritzker School of Medicine and registered at ClinicalTrials.gov (NCT01542645, principle investigator Glenn Murphy, registered 2/26/2012). Participants were recruited by reviewing operating room schedules and contact by telephone on the day before surgery. Patients presenting for elective cardiac surgery (coronary artery bypass graft [CABG] surgery, valve surgery, combined CABG/valve procedures, or atrial septal defect repair) with CPB and anticipated extubation within 12 h of surgery were enrolled. Exclusion criteria included as follows: preoperative renal failure requiring dialysis or serum creatinine greater than 2.0; significant hepatic dysfunction (liver function tests more than twice the upper limit of normal), ejection fraction less than 30%, pulmonary disease necessitating home oxygen therapy, preoperative requirement for inotopic agents or intraaortic balloon pump to maintain hemodynamic stability, emergency surgery, allergy to methadone or fentanyl, or use of preoperative opioids or recent history of opioid abuse. Patients were randomized to receive either methadone (methadone group) or fentanyl (fentanyl group) using a computer-generated randomization code; block randomization was not used. The operating room pharmacy was provided with the randomization assignment, and the study opioid was prepared in sequentially numbered, identical-appearing clear plastic bags. Either 0.3 mg/kg of methadone (maximum dose of 30 mg) or 12 μg/kg of fentanyl (maximum dose of 1200 μg) was added to 100-ml bags of normal saline (total volume 100 ml). Doses selected reflected usual intraoperative regimens that would allow for early tracheal extubation; these doses have also been demonstrated to be approximately equipotent.[20,21] All care providers and research team members were blinded to group assignment throughout the perioperative period.

Patients received 2 mg of midazolam before transport to the operating room. Monitoring consisted of a radial and pulmonary artery catheter, transesophageal echocardiography, a five-lead electrocardiogram, pulse oximetry, capnography, Bispectral Index monitoring (BIS® system; Aspect Medical Systems, USA), and cerebral oximetry (Fore-Sight®; CAS Medical Systems, USA). Anesthesia was induced with midazolam (2 to 4 mg), propofol titrated to loss of consciousness (20 to 100 mg), and rocuronium (0.6 to 0.8 mg/kg). At induction, one half of the study opioid (either 0.15 mg/kg of methadone or 6 μg/kg of fentanyl) was administered *via* an infusion pump over 5 min. The remainder of the study opioid (0.15 mg/kg of methadone or 6 μg/kg of fentanyl) was infused over the next 2 h. Maintenance of anesthesia consisted of sevoflurane 0.4 to 3.0%, which was titrated to Bispectral Index values of 40 to 60 and to mean arterial pressures (MAPs) within 20% of baseline values. Rocuronium was administered to maintain a train-of-four count less than two. Hypotension was treated with phenylephrine (80 μg), ephedrine (5 to 10 mg), or a fluid bolus, as clinically indicated. Hypertension was treated by increasing the concentration of sevoflurane, with nitroglycerin boluses (50 μg) used if MAP remained increased. 5-mg midazolam was administered during rewarming. Inotropic agents were used during separation from CPB when the cardiac index was less than 2.0 $l \cdot min^{-1} \cdot m^{-2}$ or if significant systolic dysfunction was noted on transesophageal echocardiography (dobutamine as a first-line agent, with epinephrine and milrinone used as second-line drugs). Aminocaproic acid (5-g load before skin incision, 5 g added to the pump prime, and an infusion of 1 g/h) was administered in all patients. No steroids or antiemetic agents were given perioperatively. An infusion of propofol (10 to 50 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was initiated at sternal closure and continued until ventilatory weaning in the ICU.

A median sternotomy approach was used in all subjects. In CABG patients, a left internal thoracic artery and saphenous veins were used as conduits. Mean pressures of 50 to 70 mmHg and blood flows of 2.4 to 2.8 $l \cdot min^{-1} \cdot m^{-2}$ were maintained during mild to moderate hypothermic (30° to 34°C) bypass. Isoflurane was titrated to mean systemic pressure goals and Bispectral Index values of 40 to 60 (clinicians instructed to maintain values within this range). Hematocrits were kept above 21% on CPB and above 27% postoperatively. All patients were warmed to a bladder temperature of 37°C before separation from CPB. Anticoagulation was reversed with protamine sulfate, given at a ratio of 1 mg/100 U of heparin.

Patients were assessed for pain by nurses in the ICU after the propofol infusion was discontinued and then every 2 h during the admission. 2-mg morphine was administered to patients if pain of more than mild severity was noted, with additional doses given until the patient was comfortable (verbal pain score <3 on a 0 to 10 rating scale [0 = no pain, 10 = worst pain imaginable]). Patients were typically transitioned to oral pain medication near the time of transfer to the surgical wards. Oral pain medication consisted of one 10-mg hydrocodone, 325-mg acetaminophen tablet for mild pain and two tablets for moderate pain. On the surgical ward, patients were evaluated every 4 to 6 h for pain by ward nurses, and morphine or oral pain medication was provided as needed. Postoperative analgesics were administered until the patients stated that they were comfortable and required no further pain medication. Aspirin (81 mg) was started on postoperative day 1 and continued throughout the hospitalization. Tracheal extubation, ICU discharge, and hospital discharge were accomplished when standard criteria were met (appendix).

Data Collection

All data were collected by research team members and nurses blinded to group assignment. Hemodynamic data (heart rate, MAP, mean pulmonary artery pressure, central venous pressure, systemic vascular resistance index, cardiac index, and stroke volume index) were measured at seven time periods (10 and 30 min post induction; 30 and 60 min post CPB, ICU arrival; and 4 and 8 h post ICU arrival). These measurements were recorded on a data collection sheet, as was information related to transfusions, arrhythmias, inotropic drug use, arterial blood gas analysis, and tracheal extubation. Fifteen minutes after tracheal extubation, patients were asked to quantify severity of pain using an 11-point verbal rating scale, where 0 = no pain and 10 = worst pain imaginable. Patients quantified pain intensity at rest and with coughing. The level of sedation was measured using a 4-point scale (0 = fully awake, 1 = mildly sedated [seldom drowsy and easy to awake], 2 = moderately sedated [often drowsy and easy to awake], 3 = severely sedated [somnolent and difficult to awake]). Episodes of nausea and vomiting were assessed, as were drugs used to treat nausea and vomiting. Any itching noted by the patient was recorded. Episodes of hypoventilation (respiratory rate <8) or hypoxemia (peripheral oxygen saturation <90% on pulse oximeter) observed by the nursing staff were noted. Heart rate, MAP, and peripheral oxygen saturation values were recorded at the time of pain assessment. At this same time, patients were asked to evaluate overall satisfaction with pain management on a 101-point verbal analogue scale (0 = worst possible, 100 = best possible). These same pain, sedation, nausea, vomiting, itching, ventilatory, hemodynamic, and satisfaction assessments were conducted 2, 4, 8, 12, 24, 48, and 72 h after tracheal extubation. Daily and total doses of intravenous morphine and oral 10-mg hydrocodone, 325-mg acetaminophen tablets were prospectively recorded by the nursing staff and confirmed by the research team. Whether a patient required no morphine treatment or high-dose morphine treatment (defined as ≥20 mg) during the first 24 h in the ICU was recorded.

The times from ICU admission to ventilatory weaning was initiated and tracheal extubation was achieved were recorded, as was the duration of the ICU stay. The times from ICU admission until first flatus and bowel movement were also noted. Postoperative complications were categorized as respiratory, cardiac, neurologic, renal, or infective (see appendix for specific definitions). These events were determined by the surgical service and recorded by the research team. Patient demographic data and medication lists were collected from electronic anesthesia and surgical records. The duration of hospitalization was determined in both study cohorts.

The potential cardioprotective effects of methadone were assessed by measuring serum troponin I values (marker of myocardial injury) and B-type natriuretic peptide concentrations (marker of myocardial function) in the cohort of patients undergoing only CABG procedures. Myocardial function was further evaluated by calculating cardiac and stroke volume index in the operating room and ICU. Blood samples for biochemical markers were obtained at four times: after induction of anesthesia (baseline); on arrival to the ICU; and 12 and 24 h from baseline measurements. Samples were immediately centrifuged and processed. Troponin I was measured using an immunoassay method (Beckman Coulter, USA). The limit of quantification of Troponin I was 0.03 ng/ml. Plasma B-type natriuretic peptide concentrations were also determined using an immunoassay technique (Biosite Diagnostics, USA).

Statistics

The variables of the joint primary hypothesis, decreased morphine requirements in the first 24 h after cardiac surgery and improved pain scores at 12 h after extubation, are summarized as median and interquartile range. These variables were compared between the randomized groups using the Mann–Whitney U test and median differences and their 99% CIs were calculated (StatsDirect, United Kingdom). When testing the joint hypothesis, superiority was assessed using one-tailed tests, with the criterion for rejection of the null hypothesis $P < 0.025$ without adjustment for multiple testing because intraoperative methadone administration was considered to be superior to intraoperative fentanyl administration if it both decreased

morphine requirements in the first 24 h after cardiac surgery and improved pain scores at 12 h after extubation.

In estimating the sample size needed to test our joint primary hypothesis, the criterion for rejection of the entire joint hypothesis was 0.025. A sample size of 52 patients per group gave 80% power at the 0.025 significance level to detect a clinically significant 30% reduction in morphine consumption in patients given methadone, assuming a mean of 10.7 mg in the control (*i.e.*, fentanyl) group[22] and SDs of about 6 in each group using a one-tailed Mann–Whitney test. We also had 80% power to detect a clinically significant 20% reduction in pain score, assuming a mean of 4.9 in the control group[22] and SD of about 1.9 for each group and with a significance level of 0.025 using a one-tailed Mann–Whitney test. We enrolled an additional 30 patients per group to ensure complete collection of data (including survey data on chronic postoperative pain).

Secondary outcome variables that were characterized by nominal data (*e.g.*, complications) are summarized as the number patients in each category and the percentage of all the patients in that group that they represent. These variables were compared between the randomized groups using Pearson chi-square test or, when at least one of the cells of the contingency table had an expected n < 5, Fisher exact test (NCSS, USA). Variables that were characterized by ordinal data and non-normally distributed continuous data (*e.g.*, postoperative analgesic requirements, level of pain, overall satisfaction, troponin I concentrations, and B-type natriuretic peptide concentrations) are summarized as median and interquartile range. These variables were compared between the randomized groups using the Mann–Whitney U test (StatsDirect, United Kingdom). Median differences and their 99% CIs were calculated where reported. Variables that were characterized by normally distributed continuous data are summarized as mean and SD. These variables were compared between the randomized groups using the unpaired t test (NCSS). The criterion for rejection of the null hypothesis was a two-tailed $P < 0.05$ for all between-group comparisons of secondary outcome variables, with that criterion corrected (Bonferroni) for comparing the randomized groups at multiple time points and for analyzing multiple secondary outcome variables (*e.g.*, level of pain with coughing, overall satisfaction with pain management, opioid-related complications).

Results

A total of 164 patients were enrolled in this clinical trial. Eight patients were excluded before completion of ICU data collection (protocol violations [3], surgery cancelled for a calcified aorta [1], study drug unavailable at the start of surgery [2], severe hypertension before study drug administration [1], and patient death after ICU arrival [1]). Therefore, perioperative data were available on 156 subjects. Patient characteristics are presented in table 1. Patients in the methadone and fentanyl groups did not differ strikingly in sex, age, weight, height, preexisting medical conditions, preoperative medications, baseline ejection fraction, or type of surgical procedure.

Intraoperative management of the two groups, including durations of anesthesia and CPB, administration of crystalloids and blood products, intraoperative arrhythmias and treatments, and use of vasoactive medication, did not differ (table 2). Hemodynamic variables in the operating room and ICU did not differ at any measurement time, with the exception of a higher heart rate in the methadone group 10 min (73 *vs.* 66 beats/min) and 30 min (67 *vs.* 62 beats/min) post induction, as well as a higher MAP in the methadone group 10 min (84 *vs.* 77 mmHg) and 30 min (83 *vs.* 74 mmHg) post induction (all $P < 0.001$). Central temperatures, Pa_{O_2}/FI_{O_2} (pressure of arterial oxygen/fractional inspired oxygen concentration) ratios, Pa_{CO_2} (partial pressure of arterial carbon dioxide) values, and glucose concentrations in the operating room and ICU did not differ between the groups (data not shown). The times required to wean patients off ventilatory support (median times in the methadone and fentanyl groups

Table 1. Patient Characteristics

	Methadone Group	Fentanyl Group
No.	77	79
Sex (male)	52 (67.5%)	63 (79.8%)
Age (yr)	64.7 ± 10.5	65.5 ± 11.1
Weight (kg)	87.7 ± 17.6	82.9 ± 17.3
Height (cm)	171.4 ± 9.6	173.7 ± 10.0
ASA physical status	4 (3–4)	4 (3–4)
Ejection fraction (%)	56.5 ± 13.8*	56.3 ± 11.6†
Smoking history	9 (11.7%)	12 (15.2%)
Drinking history	7 (9.1%)	6 (7.6%)
Myocardial infarction	9 (11.7%)	18 (22.8%)
Congestive heart failure	8 (10.4%)	9 (11.4%)
Atrial fibrillation	18 (23.4%)	21 (26.6%)
Hypertension	60 (77.9%)	59 (74.7%)
COPD	3 (3.9%)	5 (6.3%)
Sleep apnea	14 (18.2%)	9 (11.4%)
Thyroid disease	5 (6.5%)	12 (15.2%)
NIDDM	14 (18.2%)	19 (24.1%)
IDDM	1 (1.3%)	3 (3.8%)
Cerebrovascular accident	2 (2.6%)	0 (0%)
Transient ischemic attack	4 (5.2%)	1 (1.3%)
Peripheral vascular disease	2 (2.6%)	0 (0%)
β-Blocker	50 (64.9%)	53 (67.1%)
Calcium channel blocker	11 (14.3%)	11 (13.9%)
ACE inhibitor	34 (44.2%)	38 (48.1%)
Nitrates	12 (15.6%)	14 (17.7%)
Diuretics	24 (31.2%)	20 (25.3%)
Statins	49 (63.6%)	53 (67.1%)
Operative procedures		
CABG	35 (45.4%)	43 (54.4%)
Valve	35 (45.4%)	28 (35.4%)
CABG and valve	6 (7.8%)	6 (7.6%)
Atrial septal defect	1 (1.3%)	2 (2.5%)

Data are mean ± SD, median (interquartile range), or number of patients (%).

* n = 76; † n = 78.

ACE = angiotensin-converting enzyme; ASA = American Society of Anesthesiologists; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; drinking history = alcohol consumption > 2 drinks/day; IDDM = insulin-dependent diabetes mellitus; NIDDM = noninsulin-dependent diabetes mellitus.

Table 2. Perioperative and Postoperative Data

	Methadone Group	Fentanyl Group	*P* Value
Anesthesia time (min)	365 (324–426)	371 (331–427)	0.864
CPB time (min)	116 (98–136)	117 (99–132)	0.875
Cross clamp time (min)	88 (73–104)	84 (68–102)	0.375
Fluid volume (ml)	2516 ± 792	2574 ± 837	0.658
Packed erythrocytes (U)	0 (0–0)	0 (0–0)	0.710
FFP (U)	0 (0–0)	0 (0–0)	0.344
Platelets (U)	0 (0–0)	0 (0–0)	0.651
Urine output (ml)	980 (650–1250)	1000 (750–1300)	0.446
Arrhythmia	30 (39.0%)	33 (41.8%)	0.721
Electrical defibrillation	22 (28.6%)	27 (34.2%)	0.451
No. of defibrillations	1 (1–2)	1 (1–1)	0.040
Antiarrhythmic drug	12 (15.6%)	6 (7.6%)	0.118
Pacing	28 (36.4%)	34 (43.0%)	0.394
Inotropes	20 (26.0%)	22 (27.9%)	0.792
Vasopressor	45 (58.4%)	51 (64.6%)	0.433
Time of ventilation weaning (hr)	4.75 (3.75–7.0)	4.5 (3.75–7.0)	0.556
Time of tracheal extubation (hr)	6.5 (5.0–9.5)	6.0 (4.75–10.5)	0.693
Time of ICU discharge (hr)	30.5 (26.75–60.0)	47.13 (26.5–69.5)*	0.452
Time of first flatus (hr)	20.25 (14.25–31.25)†	26 (17.0–39.0)‡	0.327
Time of first bowel movement (hr)	71.75 (53.0–91.0)§	77 (58.5–96.0)*	0.254
Duration of hospitalization (days)	6.75 (5.0–8.0)‖	7.0 (5.75–8.0)*	0.515

Data are mean ± SD, median (interquartile range), or number of patients (%). Data reported as mean ± SD were compared using the unpaired *t* test, data reported as median (interquartile range) were compared using the Mann–Whitney U test, and data reported as number of patients (%) were compared using Pearson chi-square test. No *P* value met the criterion for rejection of the null hypothesis. n = 77 in the methadone group and n = 79 in the morphine group, except where indicated.

* n = 78; † n = 75; ‡ n = 77; § n = 74; ‖ n = 76.

CPB = cardiopulmonary bypass; FFP = fresh frozen plasma; ICU = intensive care unit

were 4.75 and 4.5 h, respectively) and to achieve tracheal extubation (median times in the methadone and fentanyl groups were 6.5 and 6.0 h, respectively) were not found to be different between the two study groups (table 2).

The variables of the joint hypothesis are presented in table 3. Patients administered methadone intraoperatively had both decreased morphine requirements in the first 24 h after cardiac surgery and improved pain scores at 12 h after extubation compared with patients administered standard doses of intraoperative doses of fentanyl.

Postoperative analgesic data are presented in table 4. The time to first morphine rescue was significantly longer in the methadone group (median, 6.5 and interquartile range, 3.25 to 9.25 h) than it was in the fentanyl group (median, 3.75 and interquartile range, 1.5 to 5.75 h) ($P < 0.001$). The requirements for morphine during the first 24 h of the ICU admission were reduced in the methadone group compared with the fentanyl group (6 [4 to 12] mg *vs.* 10 [6 to 22] mg) ($P < 0.001$). Five patients received no morphine during this time and four of the five required no morphine during the hospitalization; all five patients were in the methadone group. In contrast, significantly more patients in the fentanyl group (29.1%) required ≥ 20 mg of morphine during the first 24 h than did those in the methadone group (2.6%) ($P < 0.001$). Total morphine use over the first 72 h was less in the methadone group (8 [4 to14] mg) than it was in the fentanyl group (14 [8 to 28] mg) ($P < 0.001$). The use of oral pain medication tablets (10-mg hydrocodone, 325-mg acetaminophen) did not differ between groups during any of the three 24-h postoperative periods. Analgesic requirements, reported here, as well as pain scores and patient satisfaction related to pain management, reported in the next paragraph, after the

Table 3. Variables of the Joint Hypothesis, Morphine in the First 24 h and Level of Pain with Coughing at 12 h

	Methadone Group	Fentanyl Group	Difference (99% CI)	*P* Value
Morphine (mg)				
First 24 h	6 (4 to 12)	10 (6 to 22)	−4 (−8 to −2)	<0.001
Level of pain with coughing				
12 h	4 (3 to 5)	6 (4 to 8)	−2 (−3 to −1)	<0.001

Data are median (interquartile range). Data were compared using the Mann–Whitney U test. Both *P* values met the criterion for rejection of the null hypothesis. These data are also included in tables 4 (morphine first 24 h) and 5 (level of pain with coughing 12 h) for the sake of completeness of those data. n = 77 in the methadone group for morphine first 24 h and 74 for level of pain with coughing 12 h. n = 79 in the fentanyl group.

CI = confidence interval.

Table 4. Postoperative Analgesic Requirements

	Methadone Group	Fentanyl Group	Difference (99% CI)	*P* Value
Time of first morphine rescue (h)	6.5 (3.25 to 9.25)	3.75 (1.5 to 5.75)	2.25 (1 to 4)	<0.001
Morphine (mg)				
First 24 h	6 (4 to 12)	10 (6 to 22)	−4 (−8 to −2)	<0.001
Second 24 h	0 (0 to 2)	1 (0 to 6)	0 (−2 to 0)	0.036
Third 24 h	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0.403
Total	8 (4 to 14)	14 (8 to 28)	−6 (−10 to −2)	<0.001
Morphine dose ≥20 mg first 24 h	2 (2.6%)	23 (29.1%)	−26.5 (−41.4 to −12.9)	<0.001
Oral pain tablets				
First 24 h	2 (0 to 4)	2 (0 to 4)	0 (0 to 0)	0.859
Second 24 h	4 (2 to 8)	4 (2 to 6)	0 (−2 to 2)	0.607
Third 24 h	2 (0 to 6)	4 (0 to 8)	0 (−2 to 0)	0.130
Total	10 (4 to 16)	12 (6 to 16)	0 (−4 to 2)	0.443

Data are median (interquartile range) or number (percentage) of patients. Data reported as median (interquartile range) were compared using the Mann–Whitney U test, and data reported as number of patients (%) were compared using Pearson chi-square test. The *P* values meeting the criterion for rejection of the null hypothesis were those for time of first morphine rescue, morphine first 24 h, morphine total, and morphine dose ≥20 mg first 24 h. Morphine dose ≥ 20 mg first 24 h = number (percentage) of patients receiving this dose of morphine. Oral pain tablets = hydrocodone 10 mg/acetaminophen 325 mg. n = 77 in the methadone group. n = 79 in the fentanyl group.

CI = confidence interval.

first 24 h should be interpreted with caution because patient transition from intravenous morphine to oral hydrocodone/acetaminophen may have affected these results.

Pain scores (scale of 0 to 10) at rest were significantly less in the methadone group (medians 2 to 3) than they were in the fentanyl group (medians 3 to 5) (all P <0.001 to 0.002) during the first 72 h, with the exception of at 4 h (P = 0.012) (table 5). Similarly, pain scores with coughing (medians 4 to 5 in the methadone group, medians 5 to 7 in the fentanyl group) were less in the methadone group throughout the first 3 postoperative days (all P < 0.001). Overall satisfaction with pain management, measured on a 101-point visual analog scale, was higher in the methadone group (medians 90 to 100) than in the fentanyl group (medians 70 to 90) (all P < 0.001 to 0.006) at all measurement times except at 12 h (P = 0.025) (table 5).

Further recovery data are presented in tables 2 and 6. No differences between groups were observed in the incidences of opioid-related side effects during the first 72 h, including nausea, vomiting, itching, hypoventilation (<8 breaths/min), hypoxemia (Spo_2 < 90%), or level of sedation. No differences between groups were noted in time to first flatus and bowel movement. The median duration of ICU admission was 30.5 (interquartile range, 27 to 60) h in the methadone group and 47 (interquartile range, 27 to70) h in the fentanyl group (P = 0.452). The median duration of hospitalization was ≈7 days in both groups; the duration of hospitalization did not differ between the groups (P = 0.515). Complications observed in the postoperative period (respiratory, cardiac, neurologic, renal, or infective) did not differ between groups (table 7). These assessments of recovery data should be interpreted with caution because the study was not powered to detect differences in these variables.

Serum markers for myocardial injury (troponin I) and function (B-type natriuretic peptide) in patients undergoing CABG surgery are presented in table 8. Although serum concentrations of each biomarker increased over time, no differences between groups were noted at ICU admission or at 12 and 24 h from anesthetic induction.

Discussion

Pain is an under-recognized and under-treated problem in cardiac surgical patients.[9] Several analgesic strategies have been investigated in this patient population, including epidural or spinal anesthesia, infusions of local anesthetics in surgical incisions, and peripheral nerve blocks[23–28] However, clinicians may be reluctant to use these techniques due to potential concerns, such as bleeding, nerve injury, or sternal wound infection.[23–28] Traditionally, opioids are used to manage pain during the first 1 to 3 days after cardiac surgery. Intermittent administration of relatively short-acting opioids, such as morphine and hydromorphone, results in fluctuations in plasma concentrations, which may account for the relatively high pain scores reported in this patient population. In the current investigation, the authors found intraoperative methadone to be superior to fentanyl for patients undergoing cardiac surgery; patients in the methadone group had both decreased morphine requirements in the first 24 postoperative hours and improved pain scores 12 h after extubation compared with patients in the fentanyl group. Intravenous morphine requirements in the methadone group were reduced by 40% during the first 24 h after tracheal extubation when reported pain intensity is greatest.[2,25] In patients randomized to receive methadone, the severity of postoperative pain was decreased by ≈30 to 40% and patient-perceived quality of pain management was significantly enhanced during the first 3 days after cardiac surgery.

Patients undergoing cardiac surgery usually receive an opioid with a short duration of effect in the operating room (*e.g.*, fentanyl, sufentanil). During early emergence from anesthesia, patients may be unable to communicate any experiences of pain due to the presence of an endotracheal tube or residual neuromuscular block.[29] Upon awakening in discomfort, patients are

Table 5. Postextubation Levels of Pain at Rest and with Coughing and Overall Satisfaction with Pain Management

	Methadone Group	Fentanyl Group	Difference (99% CI)	*P* Value
Level of pain at rest				
15 min	3 (1 to 5)	5 (2 to 8)	−2 (−4 to −1)	<0.001
2 h	3 (1 to 5)	4.5 (2 to 7)*	−1 (−3 to 0)	0.002
4 h	2 (1 to 4)	3 (1 to 6)*	−1 (−2 to 0)	0.012
8 h	2 (0 to 4)	4 (2 to 6)*	−2 (−3 to 0)	<0.001
12 h	2 (0 to 4)†	4 (2 to 5)	−1 (−2 to 0)	<0.001
24 h	2 (1 to 4)†	4 (2 to 7)*	−2 (−3 to 0)	<0.001
48 h	2 (0 to 3)‡	3 (1 to 5)§	−1 (−2 to 0)	0.002
72 h	2 (0 to 3)†	3 (0 to 5)§	−1 (−2 to 0)	0.002
Level of pain with coughing				
15 min	5 (3 to 6)	7 (4 to 10)	−2 (−4 to −1)	<0.001
2 h	4 (3 to 6)	7 (4 to 8.5)*	−2 (−3 to −1)	<0.001
4 h	4 (3 to 6)	6 (4 to 8)*	−2 (−3 to −1)	<0.001
8 h	4 (2 to 5)	7 (5 to 8)*	−3 (−4 to −2)	<0.001
12 h	4 (3 to 5)†	6 (4 to 8)	−2 (−3 to −1)	<0.001
24 h	5 (3 to 6)†	7 (5 to 9)*	−2 (−3 to −1)	<0.001
48 h	4 (2 to 6)‡	6 (4 to 8)§	−2 (−3 to −1)	<0.001
72 h	4 (2 to 5)†	5 (3 to 7)§	−2 (−3 to 0)	<0.001
Overall satisfaction with pain management				
15 min	90 (75 to 95)	70 (40 to 90)	17 (5 to 30)	<0.001
2 h	90 (75 to 97)	75 (50 to 90)	10 (0 to 20)	<0.001
4 h	90 (80 to 98)	80 (60 to 90)	10 (0 to 20)	0.003
8 h	90 (80 to 100)	80 (60 to 95)	10 (0 to 20)	0.002
12 h	90 (80 to 100)†	85 (70 to 95)	5 (0 to 10)	0.025
24 h	95 (90 to 100)‡	90 (77.5 to 100)*	5 (0 to 10)	0.006
48 h	95 (90 to 100)‖	90 (75 to 100)§	5 (0 to 10)	<0.001
72 h	100 (90 to 100)	90 (80 to 100)§	5 (0 to 10)	<0.001

Data are reported as median (interquartile range) and were compared using the Mann–Whitney U test. No within group (*i.e.*, across time) comparisons have been made. All *P* values met the criterion for rejection of the null hypothesis except those for level of pain at rest 4 h and overall satisfaction with pain management 12 h. Level of pain scores on a 0 to 10 scale: 0 = no pain to 10 = worst pain imaginable. Overall satisfaction with pain management on a 0 to 100 scale (0 = worst possible to 100 = best possible). n = 75 in the methadone group and n = 77 in the morphine group, except where indicated.

* n = 76; † n = 74; ‡ n = 73; § n = 78; ‖ n = 72.

CI = confidence interval.

Table 6. Opioid-Related Complications: Nausea, Vomiting, Itching, Hypoventilation, Hypoxemia, and Sedation

	Methadone Group	Morphine Group	*P* Value
Nausea	38 (50%)	44 (56%)	0.425
Vomiting	18 (24%)	15 (19%)	0.501
Itching	17 (22%)	9 (12%)	0.073
Hypoventilation	3 (4%)	3 (4%)	>0.99
Hypoxemia	10 (13%)	6 (8%)	0.266
Sedation	63 (83%)	70 (90%)	0.216

Patients were assessed for opioid-related complications 15 min, 2, 4, 8, 12, 24, 48, and 72 h after extubation. Data are number of patients experiencing the complication at any time (%). Data were compared using Pearson chi-square test or, when at least one of the cells of the contingency table had an expected n < 5, Fisher exact probability test. No *P* value met the criterion for rejection of the null hypothesis. Hypoventilation = less than 8 breaths/min; hypoxemia = oxygen saturation <90%. n = 76 in the methadone group and n = 78 in the morphine group.

Table 7. Complications during the Hospitalization

	Methadone Group	Fentanyl Group	*P* Value
Respiratory complications	0 (0%)	1 (1.3%)*	>0.99
Cardiac complications	25 (32.5%)	20 (25.3%)	0.324
Renal complications	4 (5.2%)	4 (5.1%)	>0.99
Neurologic complications	2 (2.6%)	3 (3.8%)	>0.99
Infective complications	0 (0%)	0 (0%)	—

Data are number of patients (%). Data were compared using Pearson chi-square test or, when at least one of the cells of the contingency table had an expected n < 5, Fisher exact probability test. No *P* value met the criterion for rejection of the null hypothesis. n = 77 in the methadone group and n = 79 in the morphine group, except where indicated (see appendix for definitions of complications).

* n = 78.

transitioned to longer-acting opioids, such as morphine, which have a slow onset of effect.[12] A potential alternative strategy of opioid management in the perioperative period is administration of a single dose of methadone at the start of surgery. Methadone has a rapid onset of effect that is comparable with that of fentanyl or sufentanil[12] and does not produce adverse hemodynamic effects when given in large doses.[30] When doses of ≥ 20 mg of methadone are administered, the duration of analgesic effect approximates its 35-h half-life.[12,16] Therefore, a preoperative dose of methadone can provide analgesia throughout the surgical procedure, the period of intubation in the ICU, and the first postoperative day.

Table 8. Postoperative Troponin I and BNP Concentrations

	Methadone Group	Fentanyl Group	*P* Value
Troponin I (ng/ml)			
Baseline	0.02 (0.01–0.06)	0.01 (0.01–0.07)	0.590
On ICU arrival	2.6 (1.9–4.0)	2.7 (1.8–5.5)	0.655
Baseline + 12 h	5.4 (2.5–6.8)	4.6 (2.8–7.6)	0.664
Baseline + 24 h	3.2 (1.6–4.1)	3.3 (1.6–6.6)	0.738
BNP (pg/ml)			
Baseline	62 (32–127)	61 (31–229)	0.911
On ICU arrival	83.5 (38–150)	69 (43–224)	0.666
Baseline + 12 h	150 (95–264)	135 (74–284)	0.714
Baseline + 24 h	366.5 (225–497)	300.5 (168–490)	0.567

Data are reported as median (interquartile range) and were compared using the Mann–Whitney U test. No within group (*i.e.*, across time) comparisons have been made. No *P* value met the criterion for rejection of the null hypothesis. n = 34 in the methadone group at all times except at baseline + 24 h, when n = 32. n = 41 in the fentanyl group at all times except at baseline + 24 h, when n = 40.

BNP = B-Type natriuretic peptide; ICU = intensive care unit.

Only a few trials have studied methadone as an analgesic in surgical patients. In a series of small studies, Gourlay *et al.*[11,15,16] examined the use of methadone (20 to 30 mg) in patients undergoing general or orthopedic surgical procedures. Patients administered methadone required fewer doses of postoperative morphine, had longer median times until additional analgesics were requested (20 to 27 h), and reported low mean visual analog scale pain scores (1.5 on a scale of 10). Two more recent studies examined the efficacy of methadone in patients undergoing complex spine surgery. In adult patients given methadone or sufentanil intraoperatively, postoperative opioid requirements and pain scores were reduced by 50% at 48 h in those administered 0.2 mg/kg of methadone.[13] In a pharmacokinetic study of methadone in adolescents, methadone administration (in doses of 0.1, 0.2, or 0.3 mg/kg) did not dose dependently decrease pain scores or total opioid consumption.[14] However, children aged 3 to 7 yr undergoing major surgery randomized to receive 0.2 mg/kg of methadone reported lower pain scores and required fewer supplemental analgesic drugs than those receiving 0.2 mg/kg of morphine.[31] Furthermore, in women undergoing hysterectomies, patients given methadone (0.25 mg/kg or 20 mg) reported significantly less pain and requested less analgesic medication than those administered morphine.[32,33] No significant adverse events associated with methadone use were observed in any of the clinical trials. Although methadone appears to be an effective and safe analgesic agent, interpretation of the findings from previous studies is limited by the small size of the study samples (20 to 40 patients),[11,13–16,31–33] lack of randomization[11,14,16] or blinding,[11,13,14,16,33] or absence of a control group.[11,16]

In the current investigation, intravenous morphine requirements during the first 24 h after surgery and total doses of postoperative morphine were reduced by ≈40% in patients randomized to receive methadone; this is consistent with the "opioid sparing" effect reported from a 0.2-mg/kg dose of intraoperative methadone.[13] Nearly one third of patients in the fentanyl group required high-dose morphine (≥20 mg) for pain control during the first 24 h, whereas high-dose treatment was needed in only 2.6% of subjects in the methadone group. Similarly, the five patients requiring no morphine 24 h postoperatively had all received methadone. The long half-life and extended duration of effect of methadone likely contributed to the decreased need for analgesic medication in these patients. Furthermore, methadone has NMDA receptor antagonist activity *in vitro* and *in vivo*.[34,35] Activation of NMDA receptors has been implicated in the development of hyperalgesia, acute and chronic tolerance, and chronic pain states.[19,34,36] Methadone, *via* an inhibitory effect on the NMDA receptor, may prevent initiation of acute opioid tolerance and hyperalgesia, resulting in a decreased need for analgesics.[13,19]

In addition to reduced postoperative morphine requirements, patients in the methadone group reported lower pain scores during the first 3 postoperative days. The degree of postoperative pain in cardiac surgical patients may be influenced by age, sex, use of left internal mammary artery graft, and type of surgical procedure,[8,10,37] which were similar in the two study groups. Pain scores in the fentanyl group were comparable with those reported in other investigations using standard fast track cardiac anesthesia techniques.[2,3,25] In contrast, pain intensity at rest and with coughing was significantly less in the methadone group. Similar improvements in postoperative pain control have been reported in spinal and gynecologic surgical patients administered methadone at anesthetic induction.[13,33] Overall satisfaction with pain management was excellent in the methadone group but was less in the fentanyl group at all assessment times, except at the 12-h evaluation.

Opioid-related adverse events did not differ between the methadone and fentanyl groups. Methadone use was not associated with clinically apparent respiratory depression; neither duration of tracheal intubation nor the number of postoperative hypoxemic and hypoventilation events differed between the two groups. The incidence of nausea and vomiting in the methadone and fentanyl cohorts were not different, nor were the times to first flatus and bowel movement. Level of sedation and pruritis also did not differ between groups in the postoperative period. At the time of hospital discharge, the incidences of respiratory, cardiac, renal, neurologic, or infective complications did not differ between groups.

Epidemiologic data suggest that long-term exposure to methadone is associated with a reduced incidence and severity of coronary artery disease.[38] Animal models have demonstrated that methadone has potent cardioprotective effects. Myocardial infarct size was significantly reduced, compared with placebo, when a dose of 0.3 mg/kg was given before a period of ischemia.[17] Methadone attenuated ischemic injury to the heart *via* binding to the δ-opioid receptor.[17] In contrast, fentanyl does not appear to confer myocardial protection at clinically relevant concentrations due to its lower affinity for the δ-opioid receptor.[39,40] In the current investigation, the potential cardioprotective effects of methadone were assessed by measuring markers of myocardial injury (troponin concentrations) and cardiac function (serum B-type natriuretic

peptide levels and hemodynamic measurements) during the intraoperative and postoperative periods. No differences in any of these variables were noted between groups. There are several potential explanations for the absence of a cardioprotective effect in the methadone group. If methadone can attenuate myocardial ischemia in humans, the dose needed to do so is unknown. Furthermore, in a rat model, cardioprotection induced by methadone was inhibited when the duration of ischemia extended beyond 45 min[17]; the average duration of aortic cross clamping exceeded this threshold in both study groups. Finally, the relatively small number of patients undergoing only CABG procedures in the two groups and the relatively wide dispersion of the troponin I and B-type natriuretic peptide data limit our ability to detect a difference in these variables between groups if such a difference exists (*i.e.*, power). For example, group sample sizes of 32 and 40 achieve only 24% power to detect the observed difference in troponin I at 12 h with a significance level (α) of 0.05 using a two-sided Mann–Whitney test.

There are several limitations to this investigation. First, although the dose of methadone used in the current study was both safe and effective, the optimal intraoperative dose of methadone was not determined. Second, assessments for pain and opioid-related complications were only performed for 72 h. Third, high-risk cardiac surgical patients were excluded from enrollment. Finally, the effect of methadone on long-term chronic pain has not been reported here, but is being examined in an ongoing study.

As noted in a recent editorial on cardiac anesthesia research, "... it is time to move away from trying to prove that anesthetic interventions will reduce morbidity and mortality and to focus on tangible benefits to patients… with outcomes primarily on patient well-being (safety parameters, pain and nausea, satisfaction)."[41] The administration of 0.3 mg/kg of methadone to cardiac surgical patients at induction of anesthesia resulted in significant reductions in analgesic requirements, improvements in pain scores, and enhanced patient-perceived quality of pain management for 72 h after tracheal extubation. No adverse events related to methadone administration were observed.

Acknowledgments

Support was provided solely from institutional and/or departmental sources.

Competing Interests

The authors declare no competing interests.

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Appendix: Recovery Criteria and Definitions of Postoperative Complications

1. Criteria for tracheal extubation
   a. Hemodynamic stability
   b. Absence of uncontrolled arrhythmias,
   c. Core temperature >36°C
   d. Chest tube drainage <100 ml in the past 2 h
   e. Arterial oxygen saturation (Spo_2) >90% on a FIO_2 < 0.5
   f. Arterial pH > 7.3
   g. Responsiveness to simple commands
2. Criteria for discharge from the ICU
   a. Absence of significant arrhythmias or need for inotropic support
   b. Arterial oxygen saturation (Spo_2) > 90% on an FIO_2 < 0.5
   c. Chest tube drainage <50 ml in the past 2 h
   d. Urine output >0.5 $mL \cdot kg^{-1} \cdot ml^{-1}$
   e. Patient alert and cooperative
3. Criteria for hospital discharge: when they were
   a. Hemodynamically stable without arrhythmias
   b. Afebrile without signs of infection
   c. Able to eat, void, and defecate normally
   d. Adequately controlled pain on oral analgesics
   e. Ambulating independently with little or no assistance
4. Postoperative cardiac complications were defined as follows (definitions derived from De Hert SG *et al.*[42]) and diagnosed by the surgical team
   a. Respiratory: mechanical ventilation for >24 h or postoperative pneumonia (pulmonary infiltrate with positive microbial cultures)
   b. Cardiac: atrial fibrillation detected on 12-lead standard electrocardiogram; arrhythmia requiring treatment with electrical cardioversion or antiarrhythmic medications; myocardial infarction defined by new Q waves on the electrocardiogram or elevation of cardiac troponin values; heart failure requiring two or more inotropic medications or use of an intra-aortic balloon pump for >24 h
   c. Neurologic: stroke, defined as a new central neurological deficit; or postoperative confusion, defined as disorientation to time and/or place and inability to cooperate with simple commands.
   d. Renal: acute increase in serum creatinine of >50% or the need for dialysis
   e. Infection: wound infection requiring surgical debridement or antibiotics

FIO_2 = fractional inspired oxygen concentration; ICU = intensive care unit.

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References

1. Mueller XM, Tinguely F, Tevaearai HT, Revelly JP, Chioléro R, von Segesser LK: Pain location, distribution, and intensity after cardiac surgery. Chest 2000; 118:391–6
2. Milgrom LB, Brooks JA, Qi R, Bunnell K, Wuestfeld S, Beckman D: Pain levels experienced with activities after cardiac surgery. Am J Crit Care 2004; 13:116–25
3. Gerbershagen HJ, Aduckathil S, van Wijck AJ, Peelen LM, Kalkman CJ, Meissner W: Pain intensity on the first day after surgery: A prospective cohort study comparing 179 surgical procedures. Anesthesiology 2013; 118:934–44
4. Gélinas C: Management of pain in cardiac surgery ICU patients: Have we improved over time? Intensive Crit Care Nurs 2007; 23:298–303
5. Lahtinen P, Kokki H, Hynynen M: Pain after cardiac surgery: A prospective cohort study of 1-year incidence and intensity. Anesthesiology 2006; 105:794–800
6. Puntillo K, Weiss SJ: Pain: Its mediators and associated morbidity in critically ill cardiovascular surgical patients. Nurs Res 1994; 43:31–6
7. Roediger L, Larbuisson R, Lamy M: New approaches and old controversies to postoperative pain control following cardiac surgery. Eur J Anaesthesiol 2006; 23:539–50
8. Lay TD, Puntillo KA, Miaskowski CA, Wallhagen MI: Analgesics prescribed and administered to intensive care cardiac surgery patients: Does patient age make a difference? Prog Cardiovasc Nurs 1996; 11:17–24
9. Maxam-Moore VA, Wilkie DJ, Woods SL: Analgesics for cardiac surgery patients in critical care: Describing current practice. Am J Crit Care 1994; 3:31–9
10. Yorke J, Wallis M, McLean B: Patients' perceptions of pain management after cardiac surgery in an Australian critical care unit. Heart Lung 2004; 33:33–41
11. Gourlay GK, Willis RJ, Wilson PR: Postoperative pain control with methadone: Influence of supplementary methadone doses and blood concentration–response relationships. Anesthesiology 1984; 61:19–26
12. Kharasch ED: Intraoperative methadone: Rediscovery, reappraisal, and reinvigoration? Anesth Analg 2011; 112:13–6
13. Gottschalk A, Durieux ME, Nemergut EC: Intraoperative methadone improves postoperative pain control in patients undergoing complex spine surgery. Anesth Analg 2011; 112:218–23
14. Sharma A, Tallchief D, Blood J, Kim T, London A, Kharasch ED: Perioperative pharmacokinetics of methadone in adolescents. Anesthesiology 2011; 115:1153–61
15. Gourlay GK, Willis RJ, Lamberty J: A double-blind comparison of the efficacy of methadone and morphine in postoperative pain control. Anesthesiology 1986; 64:322–7
16. Gourlay GK, Wilson PR, Glynn CJ: Pharmacodynamics and pharmacokinetics of methadone during the perioperative period. Anesthesiology 1982; 57:458–67
17. Gross ER, Hsu AK, Gross GJ: Acute methadone treatment reduces myocardial infarct size *via* the delta-opioid receptor in rats during reperfusion. Anesth Analg 2009; 109:1395–402
18. Meyerson J, Thelin S, Gordh T, Karlsten R: The incidence of chronic post-sternotomy pain after cardiac surgery—a prospective study. Acta Anaesthesiol Scand 2001; 45:940–4
19. Mancini I, Lossignol DA, Body JJ: Opioid switch to oral methadone in cancer pain. Curr Opin Oncol 2000; 12:308–13
20. Mercadante S, Ferrera P, Villari P, Casuccio A, Intravaia G, Mangione S: Frequency, indications, outcomes, and predictive factors of opioid switching in an acute palliative care unit. J Pain Symptom Manage 2009; 37:632–41
21. Mercadante S, Villari P, Ferrera P, Casuccio A, Gambaro V: Opioid plasma concentrations during a switch from transdermal fentanyl to methadone. J Palliat Med 2007; 10:338–44
22. Murphy GS, Szokol JW, Marymont JH, Greenberg SB, Avram MJ, Vender JS, Sherwani SS, Nisman M, Doroski V: Morphine-based cardiac anesthesia provides superior early recovery compared with fentanyl in elective cardiac surgery patients. Anesth Analg 2009; 109:311–9
23. Liu SS, Block BM, Wu CL: Effects of perioperative central neuraxial analgesia on outcome after coronary artery bypass surgery: A meta-analysis. Anesthesiology 2004; 101:153–61
24. Hansdottir V, Philip J, Olsen MF, Eduard C, Houltz E, Ricksten SE: Thoracic epidural *versus* intravenous patient-controlled analgesia after cardiac surgery: A randomized controlled trial on length of hospital stay and patient-perceived quality of recovery. Anesthesiology 2006; 104:142–51
25. White PF, Rawal S, Latham P, Markowitz S, Issioui T, Chi L, Dellaria S, Shi C, Morse L, Ing C: Use of a continuous local anesthetic infusion for pain management after median sternotomy. Anesthesiology 2003; 99:918–23
26. Agarwal S, Nuttall GA, Johnson ME, Hanson AC, Oliver WC Jr: A prospective, randomized, blinded study of continuous ropivacaine infusion in the median sternotomy incision following cardiac surgery. Reg Anesth Pain Med 2013; 38:145–50
27. McDonald SB, Jacobsohn E, Kopacz DJ, Desphande S, Helman JD, Salinas F, Hall RA: Parasternal block and local anesthetic infiltration with levobupivacaine after cardiac surgery with desflurane: The effect on postoperative pain, pulmonary function, and tracheal extubation times. Anesth Analg 2005; 100:25–32
28. Chaudhary V, Chauhan S, Choudhury M, Kiran U, Vasdev S, Talwar S: Parasternal intercostal block with ropivacaine for postoperative analgesia in pediatric patients undergoing cardiac surgery: A double-blind, randomized, controlled study. J Cardiothorac Vasc Anesth 2012; 26:439–42
29. Murphy GS, Szokol JW, Marymont JH, Avram MJ, Vender JS, Rosengart TK: Impact of shorter-acting neuromuscular blocking agents on fast-track recovery of the cardiac surgical patient. Anesthesiology 2002; 96:600–6
30. Bowdle TA, Even A, Shen DD, Swardstrom M: Methadone for the induction of anesthesia: Plasma histamine concentration, arterial blood pressure, and heart rate. Anesth Analg 2004; 98:1692–7
31. Berde CB, Beyer JE, Bournaki MC, Levin CR, Sethna NF: Comparison of morphine and methadone for prevention of postoperative pain in 3- to 7-year-old children. J Pediatr 1991; 119(1 Pt 1):136–41
32. Chui PT, Gin T: A double-blind randomised trial comparing postoperative analgesia after perioperative loading doses of methadone or morphine. Anaesth Intensive Care 1992; 20:46–51
33. Richlin DM, Reuben SS: Postoperative pain control with methadone following lower abdominal surgery. J Clin Anesth 1991; 3:112–6
34. Inturrisi CE: Pharmacology of methadone and its isomers. Minerva Anestesiol 2005; 71:435–7
35. Gorman AL, Elliott KJ, Inturrisi CE: The d- and l-isomers of methadone bind to the non-competitive site on the N-methyl-D-aspartate (NMDA) receptor in rat forebrain and spinal cord. Neurosci Lett 1997; 223:5–8
36. Salpeter SR, Buckley JS, Bruera E: The use of very-low-dose methadone for palliative pain control and the prevention of opioid hyperalgesia. J Palliat Med 2013; 16:616–22

37. Meehan DA, McRae ME, Rourke DA, Eisenring C, Imperial FA: Analgesic administration, pain intensity, and patient satisfaction in cardiac surgical patients. Am J Crit Care 1995; 4:435–42

38. Marmor M, Penn A, Widmer K, Levin RI, Maslansky R: Coronary artery disease and opioid use. Am J Cardiol 2004; 93:1295–7

39. Murphy GS, Szokol JW, Marymont JH, Avram MJ, Vender JS: Opioids and cardioprotection: The impact of morphine and fentanyl on recovery of ventricular function after cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2006; 20:493–502

40. Benedict PE, Benedict MB, Su TP, Bolling SF: Opiate drugs and δ-receptor-mediated myocardial protection. Circulation 1999;100: II357–60.

41. Royse C: Epidurals for cardiac surgery: Can we substantially reduce surgical morbidity or should we focus on quality of recovery? Anesthesiology 2011; 114:232–3

42. De Hert SG, Van der Linden PJ, Cromheecke S, Meeus R, ten Broecke PW, De Blier IG, Stockman BA, Rodrigus IE: Choice of primary anesthetic regimen can influence intensive care unit length of stay after coronary surgery with cardiopulmonary bypass. Anesthesiology 2004; 101:9–20